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Dietary and stored iron as predictors of breast cancer risk: A nested case–control study in Shanghai

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Increases in risk of breast cancer in successive generations of migrants to the United States from China and rapid temporal changes in incidence rates in China following social and economic changes clearly implicate environmental factors in the etiology of this disease. Case–control and cohort studies have provided evidence that at least some of these factors may be dietary. Iron, an essential element necessary for cell function, has also been demonstrated to have potential carcinogenic and co-carcinogenic activities. Iron overload, which was previously uncommon, has become more common in the United States than iron deficiency and may be increasing in China concurrently with dramatic increases in meat consumption. A case–control study nested in a cohort of women in Shanghai, China, was conducted to evaluate possible associations between risk of proliferative and nonproliferative fibrocystic changes as well as breast cancer and dietary iron intake and plasma ferritin levels. Plasma ferritin levels and reported dietary iron intake were compared in 346 women with fibrocystic changes, 248 breast cancer cases and 1,040 controls. Increasing ferritin levels were significantly associated with increasing risk of nonproliferative fibrocystic changes (OR: 2.51, 95% CI: 1.16–5.45, p trend = 0.04). Similar, but weaker, trends were observed for proliferative changes and for breast cancer. Risk of breast cancer relative to the risk of fibrocystic changes was associated with dietary iron intake in women with nonproliferative fibrocystic changes (OR: 2.63, 95% CI: 1.04–6.68, p = 0.02). In conclusion, this study finds significant associations between iron (stored and dietary) and fibrocystic disease and breast cancer.

Key words: breast cancer; iron; ferritin; fibrocystic breast disease; breast cancer risk factors

Although mortality and incidence rates of breast cancer remain lower in China than in the United States, they have been increasing in recent decades.[1,2] These increases in rates have been correlated with changes in the Chinese diet, including an increase in consumption of fat, fruits, eggs, meat, and the percent of energy derived from animal fats, indicating a move towards a more westernized diet.[3–5] Similar dietary changes and temporal trends in breast cancer rates have been observed in Chinese migrants to the United States and other high-risk countries and in their descendents.[6–8]

Studies of foods and food groups as risk factors for breast cancer conducted in Western and Chinese populations have yielded inconsistent results; although increases in risk with high fat or meat intake have been reported by some, others report a reduction in risk with higher fruit and vegetable consumption.[7,9] Dietary intake of micronutrients, including iron, copper, zinc, vitamin E, carotenoids, fiber and vitamin C, have also been studied as potential risk and protective factors but results are inconclusive.[10–15] Results of epidemiologic studies of iron intake as a risk factor for cancer are mixed and vary depending on the type of cancer, with most studies showing no association with breast cancer.[10,13,16,17] However, one recent study showed an increase in risk of subsequent breast cancer in women with elevated breast tissue iron concentrations at the time of diagnosis with a benign breast disease.[18]

Although nonproliferative fibrocystic conditions (NPFC) have been associated with little or no increase in breast cancer risk (0–2%), proliferative fibrocystic conditions (PFC) have been associated with a 1.5- to 4-fold increase in risk of breast cancer, with the greatest increase in women with atypia.[19] Benign breast conditions impact a large number of women resulting in additional screening, an increased risk of breast cancer and in many instances pain and discomfort. However, the risk factors for these conditions remain poorly characterized. The few studies of diet and risk of NPFC or PFC have yielded inconsistent results.[20–25] Several investigators have shown higher levels of iron in cancerous breast tissue than in normal breast tissue from women with benign breast disease, but few have compared these levels to concentrations in healthy breast tissue with no known disease.[26–29] Plausible biological mechanisms have been proposed for the induction and promotion of fibrocystic breast changes and for breast carcinogenesis by iron. Iron catalyzes the formation of hydroxyl radicals which are cancer-causing agents, it suppresses host defenses allowing for proliferation of neoplastic cells, and it acts as an essential nutrient for the proliferation of tumor cells.[30–32] In the United States, high iron body stores are common for several reasons: a sizeable portion of the population ingests iron supplements, foods are enriched with iron, and meat intake is high. Hence, it is possible that any increase in risk due to high iron intake may not be readily discernable in Western populations because mean intake is uniformly high across most groups of adult women. We evaluated the relationship between iron intake and iron stores (measured as plasma ferritin) and risk of fibrocystic breast conditions and breast cancer in a largely non-iron-supplemented population of women undergoing dietary changes likely to result in greater heterogeneity of iron intake than in western countries. If iron plays a role in the etiology of breast cancer, the etiology of fibrocystic disease, or in the transition from fibrocystic disease to cancer, this could have important implications for the prevention of this disease.[27]

Material and methods

Study population

Study subjects were selected from participants in a Breast Self Examination (BSE) trial in Shanghai, China, details of which have been described previously.[33,34] Briefly, the BSE study included over 266,000 current and retired female employees of

Abbreviations: BSE, breast self examination; FFQ, food frequency questionnaire; NDS, nutrient data system; NPFC, nonproliferative fibrocystic changes; PFC, proliferative fibrocystic changes; STIB, Shanghai Textile Industry Bureau; TIBC, iron binding capacity.

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519 Shanghai Textile Industry Bureau (STIB) factories who were born between 1925 and 1958 and were permanent residents of Shanghai. Between 1989 and 1991, all eligible women completed a baseline questionnaire requesting information on most major recognized and suspected risk factors for breast cancer, including reproductive and menstrual factors, height, weight, alcohol and tobacco use, contraceptive practices and prior breast disease, as well as information on previous clinical or self breast examinations. All participants who reported a suspicious breast lump from enrollment through July 2000 were initially evaluated by medical workers in each factory, and, if indicated, referred to a surgeon at 1 of 3 STIB-operated hospitals or to other hospitals with contractual arrangements with specific factories. Pathology slides were obtained for standardized histologic diagnosis by a reference pathologist, and stage at diagnosis and tumor sizes were abstracted from medical records in Shanghai.

Diagnosis and histological classification

A single-study pathologist (ML) reviewed slides from the benign fibrocystic conditions and from the extra-tumoral tissue from the cancer cases, and classified them according to the scheme developed by Stalsberg.[35] The following features were scored on a scale of 0–3 (normal/not present, mild, moderate, florid): adenosis, sclerosing adenosis, ductal hyperplasia, apocrine metaplasia, apocrine hyperplasia, cysts, fibrosis, calcification, duct ectasia, inflammatory reaction and lactation change. Lobular atypia, ductal atypia and apocrine atypia, were scored as 0 = none, 1 = uncertain and 2 = atypical hyperplasia. For statistical analysis, all lesions were then grouped as nonproliferative (ductal hyperplasia and sclerosing adenosis with a score of 0 or 1 and no atypical hyperplasia), or proliferative (ductal hyperplasia and/or sclerosing adenosis with a score of 2 or 3 and/or atypical ductal hyperplasia, atypical lobular hyperplasia, or atypical apocrine epithelium with a score of 2).

Breast cancer and fibrocystic condition (FC) cases

Women referred to 1 of the 3 hospitals operated by the STIB for evaluation of a breast lump, and who had a breast biopsy between September 1995 and July 2000, were eligible for inclusion in case–control studies of benign and malignant breast diseases nested within the BSE trial cohort. A total of 1,429 women underwent evaluation for a breast lump during this time period, of whom 375 were diagnosed with fibroadenoma or other nonfibrocystic benign conditions, 622 were diagnosed with fibrocystic conditions and 426 with breast cancer. Of those diagnosed with breast cancer, 6 women were determined to have had a previous diagnosis with breast cancer and were not included in our analyses. Thus, of the 420 eligible women diagnosed with histologically confirmed incident breast cancer, 378 (90%) completed a food frequency questionnaire and risk factor questionnaire and had a blood specimen drawn either prior to biopsy (n = 368) or directly following surgery (n = 16). For the current analyses only the breast cancer cases with adequate extra-tumoral breast tissue available for histologic classification (n = 248, 59% of 420) were included (130 with nonproliferative changes in the extra-tumoral tissue and 118 with proliferative changes in the extra-tumoral tissue). Among the 622 women with diagnosed fibrocystic changes, 551 (88.6% of 622) agreed to complete the FFQ interview and of these 346 (62.8% of 551) had an adequate blood sample drawn and satisfactory slides (*i.e.*, at least 5 scanning power fields) for pathological review; 158 (45.7% of 346) were characterized as having nonproliferative changes (NPFC) and 188 (54.3% of 346) with proliferative changes (PFC).[12] Women undergoing breast biopsy between September 1995 and August 1997 were also enrolled in a concurrent nested case–control study of cell proliferation. Those women undergoing breast biopsy after August 1997 were recruited solely into this study.

Controls

Control women for this study were randomly selected from women in the BSE trial with no breast biopsy. For cases also enrolled in the cell proliferation study, 20 potential controls of the same age as the corresponding case, from factories with the same hospital affiliation at the start of the BSE trial as the cases' factory, were randomly selected and listed. Women were contacted, starting with the first 2 names on the list, until 2 women with the same age and if premenopausal at the same phase of the menstrual cycle as their matched case were recruited. Three hundred and sixty-seven controls were recruited in this manner (64% of the eligible women contacted). Controls for the cases that were recruited after the termination of the cell proliferation study were frequency matched to eligible cases for this study, including the cases of benign breast conditions that are not included in this report, by 5-year age group and hospital affiliation of their factories at baseline. In-person interviews were completed for 704 (82%) of 862 controls selected in this manner. In the statistical analyses for the present report, the individual matching in the first study was not retained, and the cases were compared to all interviewed controls from both studies. The same team of interviewers conducted the interviews for both controls and cases. One control woman was excluded due to a calculated daily energy intake of over 4,000 kilocalories that was considered unreliable. In addition, there was inadequate plasma available from 30 women for ferritin analyses. Thus, a total of 1,040 controls were included in our analyses.

Informed consent was obtained from each woman prior to interview. The Institutional Review Board of the Fred Hutchinson Cancer Research Center and the Station for Prevention and Treatment of Cancer of the Shanghai Textile Industry Bureau approved the study, in accordance with the assurances of the Office for Human Research Protections of the U.S. Department of Health and Human Services.

Data collection

Dietary data were collected using an interviewer-administered food frequency questionnaire (FFQ) that was validated as described previously.[9] A detailed reproductive health questionnaire was completed at the same time as the FFQ. Answers obtained from this questionnaire, rather than from the baseline questionnaire, were used in this study.

Total intake of fruits, vegetables, meat, fish, poultry and red meat was determined and each food group was divided into quartiles according to the distribution of consumption among controls. Total caloric intake was calculated based upon food and oil consumption. Recreational and occupational physical activity was based on self-reports of activity level (light, mixed, heavy) from ages 20 to 50 for each individual.

Dietary iron, calcium and vitamin C consumption were estimated based on answers provided in the FFQ. The 1991 Chinese Food Composition Table and the University of Minnesota Nutrition Coordinating Center's Nutrient Data System (NDS) were used to determine the micronutrient content of each food item, and the values for each food item were summed to estimate total dietary intake of these 3 nutrients. Portion size data was not directly assessed but was imputed based on median intake values reported by rural and urban women on the Chinese Health and Nutrition Survey.[9] One 10 mL blood sample was obtained at the time of interview. Specimens were collected into light protected tubes and processed within 5 hr of the draw.

Plasma ferritin analysis

Plasma ferritin. Plasma ferritin was measured by a 2-site immunoradiometric technique using a commercially available reagent kit, DPC Coat-A-Count Ferritin IRMA (Los Angeles, CA). Plasma samples, BioRad Laboratories (Irvine, CA) controls and 7 levels of standards in 10 μL duplicates were incubated with murine monoclonal antiferritin coated tubes where ferritin in the plasma binds to the immobilized antibody. After decanting to

remove unbound material, goat polyclonal antiferritin antibody labeled with ^{125}I was added to the tubes to bind the existing antigen–antibody complex. After incubation and removal of unbound material, the tubes were counted in a Packard Cobra II Gamma Counter. The radioactivity bound to the tube is directly proportional to the sample's ferritin concentration which is determined by a standard curve. Linearity of the assay was between 3 and 1,177 ng/mL. The intra-assay % coefficients of variation were 4.8, 4.0 and 3.2 at 54, 158 and 399 ng/mL, respectively. The inter-assay % coefficients of variation were 8.8, 8.5 and 8.6 at 56, 166 and 398 ng/mL. Proficiency testing samples from the College of American Pathologists were also analyzed. K6, K7 and K8 from the Ligand Survey 2000 gave results of 376, 70 and 437 ng/mL respectively. "All lab results" mean values from CAP were 379, 65 and 414 ng/mL, respectively.

Statistical analysis

The controls were younger than the breast cancer cases. The distribution of demographic and reproductive characteristics among the cases was therefore standardized to the age distribution of controls, using indirect adjustment methods.[36] To determine if there was a significant association between any of the potentially confounding non-iron variables and breast cancer, we used an age-adjusted conditional logistic regression model. Dietary iron and plasma ferritin values were split into quartile categories and analyzed as categorical variables. Plasma ferritin values were also log transformed to improve normality and analyzed as a continuous variable. Because cases and controls were not recruited and interviewed at an equal rate over the 5 years of data collection, we used conditional multiple logistic regression models stratified by year of interview (1995–1996, 1997, 1998–1999, 2000–2001) to calculate odds ratios (OR) as estimates of the relative risks and their 95% confidence limits (CI).[37] All models were adjusted for age, using 5-year age categories. Dietary iron intake models were further adjusted for total energy intake.[38] Correlation analysis was performed between plasma ferritin values and dietary intake of iron. All statistical analyses were performed using the Statistical Analysis System (SAS/PC V. 9.1 program, SAS Institute, Cary, NC, 2005) and tests were considered statistically significant at p value <0.05.

Potential confounding was evaluated by adding each variable independently associated with breast cancer risk, or suspected *a priori* to be related to breast cancer, to the age-adjusted model individually. In addition, we evaluated the potential confounding effect of dietary factors known to affect iron absorption (vitamin C and calcium). Family history of breast cancer, age at menarche, age at first full-term pregnancy, age at first live birth, total live births, number of prior benign breast lumps, duration of oral contraceptive use, menopausal status, years of breastfeeding, frequency of BSE practice, education, body mass index, physical activity, dietary vitamin C intake, dietary calcium intake, red meat intake and total energy intake were evaluated as possible confounders. Variables were considered confounders if they changed the estimated OR of the main independent variable by 10% or more. The significance of a trend in risk across quartile levels of iron intake and plasma ferritin was evaluated by entering quartiles of the variable into the logistic model as different values of a single ordinal variable.

Results

As shown in Table I, women with NPFC, PFC and breast cancer (with or without proliferative changes) reported lower vitamin C intake than the control women. Women with NPFC or PFC reported conducting more breast self-exams per year than both controls and breast cancer cases with nonproliferative or proliferative extra-tumoral tissue. Women with PFC reported fewer live births and fewer months breastfeeding than controls. Fewer women with NPFC were menopausal than controls or women with PFC or breast cancer. Among breast cancer cases, women with nonproliferative changes in the extra-tumoral tissue reported menarche at an earlier age and more first degree relatives with breast cancer then controls. Women with breast cancer with proliferative changes in the extra-tumoral tissue reported fewer live births, were more likely to have a family history of breast cancer, and lower total energy intake than controls. Breast cancer cases reported lower intake of calcium than controls. There was no statistically significant correlation between reported iron intake and plasma ferritin concentration (Pearson $r = -0.004$, $p = 0.88$).

As shown in Table II, women with higher plasma ferritin levels are at a significantly increased risk of NPFC (OR for highest *vs.* lowest quartile ($Q4$ *vs.* $Q1$) = 2.51, 95% CI = (1.16–5.45) p-value for trend = 0.04). Similar results are seen for PFC, and for all fibrocystic conditions combined, although they do not reach statistical significance. Relative risks of breast cancer are also greater than unity in women in the highest quartiles of plasma ferritin concentration, regardless of the proliferation status of the extra-tumoral tissue, but none of these estimates are statistically significant. In the comparisons of breast cancers with women with fibrocystic conditions, there were no statistically significant associations with ferritin levels.

In contrast, in Table III, in the comparisons between cases and controls, there are no associations between dietary iron intake and risks of fibrocystic conditions or of breast cancer. There is, however, a significant direct association between reported iron intake and risk of cancer with nonproliferative extra-tumoral changes *vs.* risk of NPFC alone (OR for highest *vs.* lowest quartile ($Q4$ *vs.* $Q1$) = 2.63, 95% CI = (1.04–6.68) p-value for trend = 0.02). Similar, but less impressive, findings are also seen for risk of all breast cancer *vs.* all fibrocystic changes (OR for highest *vs.* lowest quartile (Q4 *vs.* Q1) = 1.36, 95% CI = (0.74–2.49) p-value for trend =0.01), and for risk of breast cancer with proliferative extra-tumoral changes *vs.* PFC alone (not statistically significant).

All breast cancer models were also stratified by stage at diagnosis (stage >T3 or ≥T3). The point estimates for risk of breast cancer associated with dietary iron intake and plasma ferritin levels did not differ significantly by stage. Stratification by menopausal status was also performed because the role of iron in the pathogenesis of breast cancer may be different for premenopausal compared to postmenopausal women.[39] However, because of the small cell sizes produced the confidence intervals widened dramatically and we had inadequate power to detect any true differences by menopausal status. In the few comparisons where adequate power was available (all breast cancer *vs.* all control and all fibrocystic disease *vs.* all control), the direction and magnitude of the risk estimates did not differ appreciably among premenopausal as compared to postmenopausal women.

Discussion

In this study, associations were observed for an increase in risk of fibrocystic conditions and breast cancer with increasing plasma ferritin concentrations, although only the association between ferritin levels and NPFC reached statistical significance. There was no association observed between dietary iron intake and risk of fibrocystic conditions; however, an increase in breast cancer risk, compared to risk of fibrocystic changes alone, with increasing dietary iron intake was observed. These observations suggest a potential role for ferritin in the etiology of fibrocystic breast conditions, and a role for dietary iron intake through use of supplements or consumption of high iron foods in the progression from fibrocystic disease to breast cancer.

We found no correlation between our measure of dietary iron intake and plasma ferritin levels. This is not unexpected. Although plasma ferritin concentrations have been shown to respond to oral or parenteral administration in animal models, plasma ferritin measures iron storage and is therefore influenced by factors other than dietary iron intake, such as frequencies of phlebotomy and menstrual status.[38,40,41] Also, dietary iron intake does not

TABLE I – SELECTED CHARACTERISTICS OF CONTROLS, WOMEN WITH FIBROCYSTIC BREAST CONDITIONS AND BREAST CANCER, SHANGHAI, CHINA

	Controls (n = 1,040)		Fibrocystic breast conditions (FCD) (n = 346)						Breast cancer (BC) cases (n = 248)					
			Nonproliferative		Proliferative		All		With non-proliferative FCD		With proliferative FCD		All	
	No.	(%)	No.	(%)[1]	No.	(%)[1]	No.	(%)[1]	No.	(%)[1]	No.	(%)[1]	No.	(%)[1]
Age														
≤39	13	1.3	23	14.6	20	10.6	43	12.4	3	2.3	5	4.2	8	3.2
40–44	461	44.3	63	40.5	84	44.7	147	42.8	37	28.5	33	28.0	70	28.2
45–49	217	20.9	43	27.2	52	27.7	95	27.5	27	20.8	31	26.3	58	23.4
50–59	122	11.7	15	9.5	8	4.3	23	6.7	23	17.7	12	10.2	35	14.1
≥60	227	21.8	13	8.2	24	12.8	37	10.7	40	30.8	37	31.4	77	31.1
Number of live births														
None	37	3.6	6	3.4	10	4.7	17	4.5	7	5.3	7	5.8	14	5.3
1	701	67.7	122	65.2	149	72.7	271	66.8	63	60.7	73	70.7	136	65.1
2	120	11.6	13	8.8	13	12.5	26	11.3	32	18.9	9	6.2	41	13.4
≥3	178	17.2	14	21.7	16	10.1	30	17.4	28	15.2	29	17.5	57	16.3
Age at first live birth[2]														
≤24	264	26.4	27	26.3	31	25.7	58	25.9	36	21.7	31	22.9	67	22.0
25–29	586	58.7	98	60.0	116	60.2	214	60.2	64	59.4	54	52.7	118	56.3
≥30	149	14.9	24	13.9	31	14.1	55	14.1	21	19.1	26	25.5	47	21.8
Months of breast feeding														
Never	224	21.5	38	21.7	53	23.8	92	23.6	28	24.7	24	22.4	52	23.0
≤6	205	19.7	41	25.4	53	25.8	94	25.0	23	19.9	23	20.1	46	19.8
7–12	357	34.3	55	26.2	53	26.3	108	26.8	30	26.0	39	38.0	69	32.1
13–24	112	10.8	13	11.9	13	10.6	26	10.7	29	18.7	7	4.5	36	12.3
≥25	142	13.7	10	15.0	16	13.6	26	14.0	20	10.9	25	15.1	45	12.8
Durtion of oral contraceptive use														
Never used	950	91.4	136	85.1	170	88.7	307	86.5	114	88.0	104	88.9	218	88.6
≤1 year	34	3.3	10	8.3	9	4.3	19	6.1	8	6.4	8	6.9	16	6.7
>1 year	55	5.3	11	6.7	9	7.1	20	7.4	8	5.6	6	4.3	14	4.8
Age at first menstrual period														
≤13	167	16.1	32	14.6	30	15.3	62	14.8	27	23.9	17	13.1	44	18.7
14	200	19.3	33	16.8	52	24.5	85	23.7	18	15.2	25	24.1	43	19.7
15	205	19.7	33	20.4	36	17.6	69	20.0	36	27.0	24	21.7	60	24.1
16	216	20.8	32	16.5	30	17.4	63	17.0	26	20.4	21	14.1	47	17.6
≥17	251	24.2	27	25.4	40	25.3	67	24.6	23	13.5	31	27.1	54	19.9
Menopause														
Yes	365	35.1	27	31.7	41	34.6	68	33.6	66	37.9	49	34.6	115	35.3
Times breast self–examination per year														
Never	706	67.9	59	42.1	75	43.6	135	42.7	66	51.1	68	54.3	134	52.8
1–6	136	13.1	29	12.9	30	14.0	59	14.1	27	22.0	25	21.3	52	21.1
7–12	191	18.4	66	43.1	77	39.6	143	40.6	34	24.7	24	23.2	58	24.3
≥13	7	0.7	3	2.0	6	2.9	9	2.7	3	2.3	1	1.3	4	1.8
First degree family history of breast cancer														
Yes	17	1.6	6	2.6	6	3.7	12	3.3	8	6.2	5	4.0	13	5.0
Education														
Elementary school or less	197	19	11	16.4	16	14.3	27	14.8	39	21.3	27	16.7	66	19.1
Middle school	812	78.2	136	77.2	163	80.4	300	79.3	83	74.7	81	74.6	164	74.7
College	30	2.9	10	6.5	9	5.4	19	6.0	8	4.1	10	8.8	18	6.2
Body mass index (kg/m^2)														
≤20	196	18.9	44	24.1	42	17.8	86	20.9	19	16.1	22	18.4	41	17.2
21–25	609	58.6	91	58.5	110	58.0	202	58.2	79	61.7	67	60.1	146	61.1
>25	235	22.6	22	17.6	36	24.4	58	20.8	32	22.2	29	21.6	61	21.7

TABLE I – SELECTED CHARACTERISTICS OF CONTROLS, WOMEN WITH FIBROCYSTIC BREAST CONDITIONS AND BREAST CANCER, SHANGHAI, CHINA (CONTINUED)

	Controls (n = 1,040)		Fibrocystic breast conditions (FCD) (n = 346)						Breast cancer (BC) cases (n = 248)					
			Nonproliferative		Proliferative		All		With non-proliferative FCD		With proliferative FCD		All	
	No.	(%)	No.	(%)[1]	No.	(%)[1]	No.	(%)[1]	No.	(%)[1]	No.	(%)[1]	No.	(%)[1]
Physical activity														
Light	189	18.2	45	29.5	47	25.7	93	27.4	31	24.4	30	24.5	81	24.5
Moderate	780	75	105	66.0	134	71.4	239	69.0	96	74.0	81	70.2	177	72.0
Heavy	71	6.8	7	4.6	7	2.9	14	3.6	3	1.6	7	5.3	10	3.5
Vitamin C intake/ day (gm)														
≤54.8	260	25	51	35.3	67	38.1	118	36.5	44	31.8	43	35.2	87	33.6
>54.8–73.4	261	25.1	33	19.3	48	23.0	81	21.3	27	18.0	35	30.2	62	24.2
>73.4–96.4	259	24.9	35	22.7	36	18.5	71	20.4	29	24.8	18	20.4	47	20.8
>96.4	260	25	38	22.8	37	20.5	76	22.0	30	25.4	22	17.5	52	21.4
Calcium intake/ day (mg)														
≤311.2	260	25	37	24.2	52	38.1	106	32.1	48	35.2	40	32.7	88	34.2
>311.2–429.1	260	25	40	23.6	52	15.2	70	18.8	27	23.1	30	26.1	57	24.7
>429.1–568.7	260	25	45	31.3	42	24.7	92	27.2	28	19.7	24	21.8	52	20.7
>568.7	260	25	35	21.1	42	22.2	78	22.0	27	22.0	24	19.5	51	20.4
Energy intake/ day (kcal)														
≤1647.2	255	24.5	46	31.4	58	32.0	104	31.1	41	29.6	41	33.4	82	31.5
>1647.2–1868.4	263	25.3	40	24.4	45	21.2	85	23.3	23	17.8	31	27.9	54	22.6
>1868.4–2128.2	261	25.1	37	25.5	48	27.2	85	26.3	28	23.6	27	23.4	55	23.4
>2128.2	261	25.1	34	18.8	37	19.6	72	19.3	38	29.2	19	15.4	57	22.6

[1]Indirect age-adjusted percentages based on age distribution of the controls.–[2]Among women with a live birth.

necessarily reflect the amount of iron that is absorbed into the body because different forms of iron have different absorption rates. While about 30% of heme iron is absorbed, less than 10% of the non-heme iron is absorbed. Most iron is recovered from the breakdown of old red blood cells, and only a small amount of iron enters and leaves the body each day. Once iron is stored as ferritin, much of it is accessible for metabolic needs.[42] This suggests that dietary iron and ferritin levels may have different effects on breast cancer risk.

It is therefore not surprising that our results differ for dietary iron and plasma ferritin. Iron stores, as measured by ferritin levels, probably are a better indicator of long term exposure of the mammary epithelial tissue to iron than is dietary iron; and our results therefore suggest that chronic exposure to increased level of iron may enhance the development of FCC. The association of dietary iron (but not of plasma ferritin levels) with an index of progression from FCC to breast cancer remains unexplained. Perhaps, dietary iron is a surrogate for other dietary factors responsible for this association, such as red meat intake. In this population, meat intake was significantly correlated with total iron intake ($r = 0.42$, $p < 0.0001$). However, when meat consumption was included as a covariate in the iron models it did not alter the OR for iron by greater than 10%, suggesting that the effect of total iron intake on risk of breast cancer may not be explained entirely by the consumption of meat.

Though the etiology of the progression from PFC to breast cancer remains poorly understood, women diagnosed with PFC have been shown to have up to a 4-fold increase in risk of breast cancer.[19] Assuming that cells undergo an initiating event that results in a proliferative advantage, continued expansion of this cell type would result in increased likelihood for the development of cancer. Theoretically, one can assume that factors associated with the onset of hyperplasia would be observed in both proliferative benign conditions and breast cancer, whereas those acting to increase the probability that proliferative disease progresses to breast cancer would be observed only in relation to breast cancer. Hence, comparison of breast cancer cases with proliferative extra-tumoral tissue to women with PFC alone may provide an indirect indicator of the possible role of dietary variables (or other factors) in the progression from PFC to breast cancer. This study provides support for iron, measured as serum ferritin, as one of these dietary variables.

Although past epidemiologic studies have not consistently shown an association between risk of breast cancer or fibrocystic breast conditions and iron intake or plasma ferritin levels, there is support in the literature for the role of iron and ferritin in the development of breast cancer, as was observed in this study.[10,13,16–18,43] Results of *in vivo* and *in vitro* experimental studies provide a plausible biological mechanism for increased ferritin levels as a risk factor for breast cancer. Iron may be carcinogenic in several ways: it catalyzes the formation of hydroxyl radicals which are cancer-causing agents, it suppresses host defenses allowing for proliferation of neoplastic cells and it acts as an essential nutrient for the proliferation of tumor cells.[30–32] These observations are especially relevant to breast tissue, which is an estrogen target tissue, because redox cycling of estrogen metabolites releases Fe^{2+} from ferritin, which generates a hydroxyl radical that may contribute to tumor initiation.[27,44,45] In rats and mice, iron has been shown to induce tumors both at the injection site and at secondary locations including mammary tissue.[31,46–51] In cell culture, cellular deprivation of both iron and transferrin led to reduced proliferation rates.[52] In addition, iron depletion caused by a low-iron diet or by an iron chelator has been shown to inhibit cancer growth through apoptosis or other means in mice and cell culture.[31,53–56] In human studies, high levels of iron, measured as plasma iron, transferrin saturation and total iron binding capacity (TIBC), have been associated with an increase in overall cancer risk[57–60] and an increase in the risk of dying from any type of cancer.[14,60] In the past studies, no significant association with breast cancer risk was observed with

TABLE II – ODDS RATIOS FOR RISK OF PROLIFERATIVE AND NONPROLIFERATIVE FIBROCYSTIC CHANGES (FCs) AND CANCER WITH PLASMA FERRITIN CONCENTRATIONS, SHANGHAI, CHINA

Quartiles (*Q*) of plasma ferritin (ng/mL)	No. of women (%)[1]			FCs *vs.* controls		Cancer *vs.* controls		Cancer *vs.* FCs	
	Control	FC	Cancer	OR[2]	95% CI	OR[2]	95% CI	OR[2]	95% CI
Plasma Ferritin									
Nonproliferative									
*Q*1 (≤18.9)	260 (25.0)	29 (18.4)	23 (17.7)	1.00		1.00		1.00[3]	
*Q*2 (>18.9–46.1)	260 (25.0)	49 (31.0)	25 (19.2)	2.03	1.09–3.77	1.35	0.67–2.74	0.56	0.26–1.21
*Q*3 (>46.1–101.9)	260 (25.0)	50 (31.7)	36 (27.7)	1.64	0.89–3.02	1.30	0.67–2.52	0.53	0.24–1.14
*Q*4 (>101.9)	260 (25.0)	30 (19.0)	46 (35.4)	2.51	1.16–5.45	1.98	0.92–4.26	0.44	0.17–1.12
	1,040 (100)	158 (100)	130 (100)						
p trend					0.04		0.11		0.09
Log ferritin				1.27	1.03–1.59	1.29	1.02–1.62	0.94	0.72–1.22
Proliferative									
*Q*1 (≤18.9)	260 (25.0)	49 (25.1)	28 (23.7)	1.00		1.00		1.00	
*Q*2 (>18.9–46.1)	260 (25.0)	50 (26.6)	30 (25.4)	1.06	0.58–1.96	1.35	0.68–2.70	1.01	0.52–1.97
*Q*3 (>46.1–101.9)	260 (25.0)	48 (25.5)	19 (16.1)	0.81	0.44–1.47	0.57	0.27–1.21	0.47	0.21–1.02
*Q*4 (>101.9)	260 (25.0)	41 (21.8)	41 (34.8)	2.04	0.93–4.46	1.53	0.69–3.37	0.62	0.28–1.39
	1,040 (100)	188 (100)	118 (100)						
p trend					0.36		0.69		0.12
Log ferritin				1.16	0.93–1.44	1.10	0.87–1.40	0.84	0.66–1.07
Total									
*Q*1 (≤18.9)	260 (25.0)	78 (22.5)	51 (20.6)	1.00		1.00		1.00	
*Q*2 (>18.9–46.1)	260 (25.0)	99 (28.6)	55 (22.2)	1.42	0.87–2.33	1.43	0.82–2.49	0.82	0.50–1.35
*Q*3 (>46.1–101.9)	260 (25.0)	98 (28.3)	55 (22.2)	1.06	0.65–1.74	0.93	0.54–1.62	0.60	0.36–1.02
*Q*4 (>101.9)	260 (25.0)	71 (20.5)	87 (35.1)	1.86	1.01–3.43	1.77	0.96–3.27	0.65	0.36–1.17
	1,040 (100)	346 (100)	248 (100)						
p trend					0.17		0.18		0.08
Log ferritin				1.17	0.98–1.39	1.20	1.00–1.44	0.89	0.75–1.06

[1]Women with missing data were excluded from the analysis.–[2]Adjusted for age and stratified by year of blood draw.–[3]Adjusted for menopausal status.

TABLE III – ODDS RATIOS FOR RISK OF PROLIFERATIVE AND NONPROLIFERATIVE FIBROCYSTIC CHANGES (FCs) AND CANCER WITH DIETARY IRON INTAKE, SHANGHAI, CHINA

Quartiles (*Q*) of iron intake (mg)	No. of women (%)[1]			FCs *vs.* controls		Cancer *vs.* controls		Cancer *vs.* FCs	
	Control	FC	Cancer	OR[2]	95% CI	OR[2]	95% CI	OR[2]	95% CI
Dietary iron									
Nonproliferative									
*Q*1 (≤12.0)	260 (25.0)	42 (26.6)	37 (28.5)	1.00[3,4,5]		1.00[4,6]		1.00[5]	
*Q*2 (>12.0–14.6)	260 (25.0)	36 (22.8)	21 (16.2)	0.82	0.42–1.62	0.77	0.37–1.60	0.80	0.36–1.80
*Q*3 (>14.6–17.5)	260 (25.0)	41 (26.0)	35 (26.9)	0.89	0.43–1.87	1.54	0.66–3.57	2.37	1.01–5.58
*Q*4 (>17.5)	260 (25.0)	39 (24.7)	37 (28.5)	0.46	0.21–1.05	0.75	0.28–2.00	2.63	1.04–6.68
	1,040 (100)	158 (100)	130 (100)						
p trend					0.08		0.70		0.02
Proliferative									
*Q*1 (≤12.0)	260 (25.0)	52 (27.7)	36 (30.5)	1.00[4,6]		1.00[4]		1.00[6]	
*Q*2 (>12.0–14.6)	260 (25.0)	52 (27.7)	30 (25.4)	1.26	0.61–2.58	0.83	0.41–1.67	1.12	0.52–2.43
*Q*3 (>14.6–17.5)	260 (25.0)	42 (22.3)	21 (17.8)	1.17	0.48–2.89	0.85	0.39–1.87	1.00	0.38–2.63
*Q*4 (>17.5)	260 (25.0)	42 (22.3)	31 (26.3)	0.70	0.25–1.92	0.89	0.40–1.95	1.59	0.57–4.44
	1,040 (100)	188 (100)	118 (100)						
p trend					0.38		0.82		0.40
Total									
*Q*1 (≤12.0)	245 (25.0)	94 (27.2)	73 (29.4)	1.00[4,5,6]		1.00[4]		1.00[5]	
*Q*2 (>12.0–14.6)	246 (25.0)	88 (25.4)	51 (20.6)	1.06	0.59–1.90	0.74	0.42–1.29	0.89	0.54–1.48
*Q*3 (>14.6–17.5)	245 (25.0)	83 (24.0)	56 (22.6)	1.00	0.50–2.02	1.21	0.67–2.21	1.12	0.63–1.97
*Q*4 (>17.5)	246 (25.0)	81 (23.4)	68 (27.4)	0.56	0.25–1.26	0.96	0.53–1.77	1.36	0.74–2.49
	982 (100)	346 (100)	248 (100)						
p trend					0.14		0.81		0.01

[1]Women with missing data were excluded from the analysis.–[2]Adjusted for age and stratified by year of blood draw.–[3]Adjusted for menopausal status.–[4]Adjusted for dietary vitamin C intake.–[5]Adjusted for dietary calcium intake.–[6]Adjusted for total energy intake.

increased iron levels, as measured by dietary iron intake, plasma iron and transferrin concentrations, TIBC or iron content in toenail clippings.[10,13,16,61] One study showed dietary iron intake to be significantly associated with a reduced risk of breast cancer,[40] another showed a positive correlation between plasma ferritin and breast cancer risk[62]; and heterozygous carriers for the allele associated with hereditary hemochromatosis, a disease characterized by iron overload, also have been associated with an increased risk of breast cancer.[63] This study does not support a direct association between ferritin and breast cancer; however, it does add to the current literature in that it suggests a role of ferritin in the risk of NPFC, and iron in the progression of fibrocystic disease to breast cancer.

Major strengths of this study are the large study population used, the wide range of dietary iron intake recorded (4.7–34.3 mg) and the use of both a plasma biomarker of iron and a dietary measure. Plasma ferritin levels were chosen as a measure of body iron stores because previous studies have shown that

ferritin is the best single indicator of iron stores.[64] Nonetheless, day-to-day variation exists in ferritin levels and therefore single plasma sample measurements may not accurately reflect average iron stores.[65,66] Plasma ferritin levels may also be elevated to a degree that is disproportionate to iron stores in instances of inflammation, liver disease, leukemia, Hodgkin's disease and increased red cell turnover.[40,67] However, this is an unlikely explanation for the observed results because any undetected disease would likely have been distributed in equal proportions in cases and controls.

Another strength of our study was our ability to account for a number of potential confounders that were not included in some previous studies. Furthermore, we had the capacity to allow for analysis of potential effect modification by cancer stage. We also attempted to stratify our results by menopausal status because estrogen has been shown to stimulate iron uptake and metabolism and blood loss is prevalent in pre-menopausal women.[27] However, there was inadequate power to detect any true differences by menopausal status. Finally, differences between cases and controls could have been a result of the influence of the breast cancer or fibrocystic disease on plasma ferritin levels or reported iron intake. However, the magnitude of our observed associations with breast cancer did not differ by the stage of the disease at diagnosis, suggesting that the presence of breast cancer did not influence iron stores, or reporting of dietary iron intake.

The questionnaire used to determine dietary intake in this study is limited by the method of portion size estimation which does not take into account possible individual variation, and therefore may not accurately reflect each individual's consumption of dietary iron.[9] Although assessment of portion size may improve the precision of the estimated intake, it has been shown that frequency of intake, not portion size, explains most of the variation in intake.[38] Additionally any misclassification would likely be similar for cases and controls, and only bias the OR estimates toward unity. In addition, as with all case–control studies, the estimate of dietary iron intake may be subject to differential reporting by cases and controls. However, in most instances we interviewed women prior to their breast biopsy, which would minimize differences in responses of women with benign and malignant disease.

In summary, iron stores, as measured by plasma ferritin concentration, may enhance the risk of fibrocystic changes in the mammary epithelium, and dietary iron intake, or other factors correlated with this intake, may increase the risk of progression of these lesions to breast cancer. Our observations are consistent with *in vitro* and *in vivo* studies suggesting a role of iron in the development of breast cancer.

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